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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/204,427	12/03/1998	HEDI HADDADA	8076.102USC1	5504

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/204,427	HADDADA ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-18 and 23-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18 and 23-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 25 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-2-03 has been entered.

The amendment filed 3-4-03, paper number 36, has been entered. Applicant's arguments filed 3-4-03 have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claim has 26 been added. Claims 15-18 and 23-26 are pending and under consideration in the instant invention.

Claim Rejections - 35 USC § 112

1. Claims 15-18 and 23-25 remain rejected and claim 26 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

Claims 15, 18, 24 and 25 are rejected because the phrase "promoter present in said replication-defective adenoviral vector or an exogenous promoter" does not have support in the specification as originally filed. Applicants point to pg 14 for support. Pg 14 contemplates

replacing the adenovirus major late promoter with a ubiquitous but exogenous promoter (line 4) or the early promoter of the E1A region of the adenovirus (line 22), while the claim encompasses using any promoter that is exogenous or endogenous to the adenovirus. The promoters in the claims are broader than those contemplated in the specification as originally filed. The claims are not limited to replacing the major late promoter with an exogenous promoter or to the E1A promoter. Therefore, the language in the claims does not have support in the specification as originally filed.

Claims 15 and 26 are new matter. Applicants point to pg 13, line 4, for support for "tumor regression of 40-50%". However, pg 13, line 4, describes the results of administering a vector encoding IL-2 into the tumor while the claims encompass using a vector encoding IL-2 or γ-INF. Obtaining tumor regression of 40-50% does not have support in the specification as originally filed using adenovirus encoding γ-INF as claimed.

Claim 25 remains new matter. Applicants point to pg 8, line 9, which contemplates inserting one or more nucleic acids into the genome. However, the citation does not state the "one or more nucleic acids" being inserted encode cytokines. While pg 14, line 27, through pg 15, line 1, contemplates "simultaneous expression of several cytokines genes" in one adenoviral vector, the citation does not state they are several different cytokines. It would not have been readily apparent to one of skill in the art to go to pg 4, lines 2-14, and pick out IL-2 and GM-CSF as claimed. Nor does the specification state the IL-2 coding region is placed after the GM-CSF coding region as claimed; applicants have not argued this aspect of the rejection.

2. Claims 15-18 and 23-25 remain rejected and claim 26 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

The specification as originally filed does not provide adequate written description for replication defective adenoviruses encoding IL-2, γ-INF or GM-CSF operatively linked to an exogenous promoter or a promoter present in the adenovirus used to treat a tumor in a patient. An adequate written description of such adenoviruses requires more than a mere statement that it is part of the invention and reference to a potential method for making it; what is required is a description of the promoters and a description of how to make the adenovirus. It is not sufficient to define an adenoviral vector for gene therapy solely by its principal biological property, i.e. to treat a tumor in a patient when injected intratumorally or into cells that infiltrate tumors, because disclosure of no more than that is simply a wish to identify adenoviral vectors with the DNA encoding the cytokine operably linked to an early or "heterologous" promoter having that biological property. Thus, claiming all replication defective adenoviral vectors encoding a cytokine operably linked to an early promoter or "heterologous" promoter that are able to treat a tumor without defining the promoters or how to make such vectors is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Likewise the specification does not provide adequate written description for replication defective adenoviruses encoding GM-CSF and IL-2 used to treat a tumor in a patient. The specification does not teach a vector encoding two copies of one cytokine, two different cytokines or how the copies are operably linked to promoters. The specification does not teach the combination of cytokines in a vector required to treat tumors administered as claimed or the resulting therapeutic effect. An adequate written description of such adenoviruses requires more than a mere statement that it is part of the invention and reference to a potential method for making it; what is required is a description of the combination of elements and a description of the resulting effect. Therefore, claim 25 lacks written description.

Applicants argue the examiner has failed to consider pg 9-15 and Fig. 1, which teach how to make various adenoviral vectors. Applicants argument is not persuasive. The rejection is not based on how to make the host of vectors encompassed by the claims. The basis of the rejection is that adenoviral vectors encoding cytokines operably linked to a promoter that are capable of treating tumors as claimed are not adequately described in the specification, and is clearly set forth in the reiterated paragraph above. Adenoviral vectors encoding IL-2 or γ-INF operably linked to a promoter present in the adenovirus or an exogenous promoter that are capable of treating tumors were not well-established. Procedures for administering adenoviral vectors encoding cytokines operably linked to a promoter present in the adenovirus or an exogenous promoter capable of treating tumors were not well-established. Adenoviral vectors encoding GM-CSF capable of treating tumors, and methods of using such vectors to treat tumors were not

well-established. The mere suggestion of replacing the adenoviral late promoter with the CMV, RSV or E1A promoter (pg 14) is not adequate guidance for one of skill to use the vector to treat tumors as claimed. The specification does not even mention an adenoviral vector encoding GM-CSF. As such, the claims remain rejected for reasons of record.

3. Claims 15-18 and 23-25 remain rejected and claim 26 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering a replication-defective adenoviral vector intratumorally to a patient such that growth of the tumor is inhibited, wherein said vector encodes IL-2 or γ-INF operably linked to the adenoviral late promoter, does not reasonably provide enablement for using an adenoviral vector encoding GM-CSF to treat tumors, using any "promoter present in said replication-defective adenoviral vector" or "exogenous" promoter, the CMV promoter or the E1A promoter to treat tumors in context of the claim, or an adenoviral vector encoding GM-CSF and IL-2 to treat tumors as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The combination of promoter, DNA encoding a cytokine and route of administration required to obtain a therapeutic effect against a tumor using adenoviral gene therapy *in vivo* was unpredictable at the time the invention was made. Miller (1995, FASEB J., Vol. 9, pages 190-199) reviewed adenoviral vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have

to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 192, col. 2; page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy continues to be the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviewed adenoviral vectors known in the art for use in gene therapy and discusses problems associated with them (page 241, col. 1). Verma indicated a resolution to vector targeting has not been achieved in the art (see entire article). Crystal (1995, Science, Vol. 270, page 404-410) also reviewed adenoviral vectors known in the art and indicated that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (para. bridging pages 404-405; page 406, col. 2, line 7; page 409).

Viral vectors encoding IL-2 and γ-INF administered intratumorally to inhibit tumor growth were known in the art at the time the invention was made (Nabel, US Patent 6,297,219, Oct. 2, 2001; Barber, US Patent 5,662,896, Sept. 2, 1997). Replication defective adenoviral vectors encoding protein operably linked to the late promoter used to obtain protein expression *in vivo* were known in the art at the time the invention was made (Crystal, US Patent 6,013,638, Jan. 11, 2000; Rosenfeld, 1991, Science, Vol. 252, pages 431-434). The art at the time of filing did not teach administering adenoviral vectors *in vivo* by any mode of delivery such that "cells

which infiltrate said tumor" were targeted, infecting "cells which infiltrate said tumor" *ex vivo* with an adenoviral vector and administering the cells into the patient such that a therapeutic effect was obtained, using a vector encoding IL-1, IL-3, IL-4, IL-5, IL-6, α-INF, TNF or CSF to treat tumors, or using an adenoviral vector encoding the cytokine operably linked to an early or "heterologous" promoter to treat tumors.

The specification teaches direct injection of "the vector" carrying IL-2 into tumors leads to tumor regression (para. bridging pages 12 and 13) which is assumed to be the adenovirus encoding a cytokine operably linked to the late promoter described in the paragraph bridging pages 9 and 10. The specification does not teach administering a viral vector into a remote site such that cells that infiltrate the tumor are targeted. Nor does the specification teach administering a viral vector into a remote site or directly injecting cells infected *ex vivo* into a tumor such that a therapeutic effect is obtained. Without such guidance, it would require one of skill undue experimentation to determine modes of delivery other than intratumoral injection that target tumor cells and provide a therapeutic effect.

The specification does not enable using a adenoviral vector encoding GM-CSF (claim 24) to treat tumors because the specification does not teach the level of GM-CSF required to obtain a therapeutic effect or correlate the level of expression of IL-2 or γ-INF known in the art to inhibit tumor growth with the level of GM-CSF required to obtain an equivalent effect. Without such guidance, it would require one of skill undue experimentation to determine how to use any cytokines other than IL-2 or γ-INF to treat tumor cells as claimed.

The specification does not enable one of skill in the art at the time the invention was made to use an adenoviral vector comprising DNA encoding a IL-2 or γ-INF operably linked to an adenoviral "heterologous" promoters (claims 15 and 24) or CMV (claim 23) to treat tumors. The specification lists the RSV LTR, the IE promoter of CMV, and MMTV or metallothionin inducible promoters as possible replacements for the adenovirus late promoter (pg 14, lines 4-11). However, the specification and the art at the time of filing did not teach the RSV LTR, the IE promoter of CMV, MMTV or metallothionin inducible promoters provided adequate expression of a protein in an adenoviral vector used *in vivo* to obtain a therapeutic effect. Nor does the specification correlate the amount of expression obtained using the adenoviral late promoter to expression obtained using the RSV LTR, the IE promoter of CMV, and MMTV or metallothionin inducible promoters such that equivalent levels of expression would be expected. Therefore, the specification does not overcome the unpredictability in the art regarding the promoter to use with adenoviral vectors administered into a tumor that provided a therapeutic level of expression of a protein. While a showing of an equivalent expression of a cytokine using promoters other than the late promoter is not necessary to achieve a therapeutic effect, in view of the unpredictability in the art regarding promoters used to target specific tissues for gene therapy, and the lack of teachings in the art regarding using these promoters with adenoviral vectors to obtain a therapeutic effect *in vivo*, the specification must provide some correlation between the late promoter and other promoters to enable a claim encompassing using any "endogenous or

heterologous promoter" in an adenoviral vector to treat tumors. Such a correlation cannot be found in the instant specification.

The specification does not teach a vector encoding GM-CSF and IL-2 (claim 25) or how the DNA encoding the cytokines are operably linked to promoters. The specification does not teach the combination of cytokines required to treat tumors using adenoviral vectors administered as claimed or the resulting therapeutic effect. Enablement of such adenoviruses requires more than a mere statement that it is part of the invention and reference to a potential method for making it; what is required is adequate guidance regarding the combination of elements and the resulting effect. Without such guidance, it would have required one of skill undue experimentation to determine how to use an adenoviral vector encoding two or more cytokines to treat tumors.

Applicants argument regarding the level of skill in the art being high for making adenoviruses (pg 10-11 of response) is off point. The rejection is based on how to use adenoviruses encoding proteins of interest for therapy, not how to make them. The level of skill in the art for using adenoviruses encoding cytokines for tumor therapy was not high at the time the invention was made as established by Crystal ('638) and Rosenfeld in view of Crystal, Deonarain, Miller and Verma, all of record.

Applicants argument regarding Crystal is off point because Crystal did not teach how to use adenoviral vector to treat tumors; Crystal taught using adenovirus encoding CFTR to increase Cl- in the lung by direct administration to the lung. None of the references of record taught how

to use any vector encoding GM-CSF to treat tumors. No correlation between IL-2 or γ-INF and GM-CSF has been provided. No correlation between adenovirus late promoter and CMV promoter or any other promoter has been provided. Given the unpredictability in the art, the specification must provide the essential information required to perform the method claimed using GM-CSF. Without such guidance, it would require one of skill undue experimentation to determine how to use the method as broadly claimed.

The paragraph at the bottom of pg 10 of the response has numerous grammatical errors and cannot be understood.

Applicants argument regarding measuring the amount of GM-CSF expression in the host is not persuasive. Applicants have provided no teachings as to what levels of GM-CSF are required to cause tumor regression as claimed, that such levels are obtainable using adenoviral vectors described in the specification or what type of promoter is required to obtain such a level of expression. Given the unpredictability in the art, these parameters are essential to practice the claimed invention. Without such guidance, it would require one of skill undue experimentation to determine how to cause tumor regression using an adenovirus encoding GM-CSF as claimed.

The specification does not enable using any promoter as claimed such that therapeutic levels of expression of IL-2 or γ-INF could be obtained *in vivo*. The specification lists the E1A promoter as a possible replacement for the adenovirus late promoter (pg 14, lines 16-22). However, the specification and the art at the time of filing did not teach the E1A promoter provided adequate expression of a protein in an adenoviral vector used *in vivo* to obtain a

therapeutic effect. Nor does the specification correlate the amount of expression obtained using the adenoviral late promoter to expression obtained using the E1A promoter such that equivalent levels of expression would be expected. Therefore, the specification does not overcome the unpredictability in the art regarding the promoter to use with adenoviral vectors administered into a tumor that provided a therapeutic level of expression of a protein. While a showing of an equivalent expression of a cytokine using promoters other than the late promoter is not necessary to achieve a therapeutic effect, in view of the unpredictability in the art regarding promoters used to target specific tissues for gene therapy, there must be some correlation between the late promoter and the E1A promoter to enable a claim reciting using any promoter to treat tumors.

4. Claims 15-18 and 23-25 remain rejected and claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claim 15 remains and claims 24 and 26 are indefinite because "said adenovirus" lacks antecedent basis.

Claims 15 and 26 are indefinite because the metes and bounds of when a pharmaceutical composition "leads" to tumor regression cannot be determined. The term "leads" does not clearly set forth that the pharmaceutical composition is responsible for or cause the regression of tumor.

Claims 15 and 24-26 are indefinite because the method is directed to treating a tumor in a patient, but results in regression of tumors in 40-50% of patients. Only one patient is injected

intratumorally with the vector in the claim, yet the claim results in the treatment of more than one patient. The results are not commensurate in scope with injecting a vector into the tumor of a patient as claimed.

Claims 15, 18 and 24-26 are indefinite because "exogenous" is unclear. The term "exogenous" is a relative term and has various meanings depending upon to what it refers. In the specification, the term refers to an adenoviral promoter being replaced with an exogenous promoter (pg 14). However, the promoter may also be exogenous to the patient or to the DNA encoding the cytokine. Therefore, it cannot be determined if the "exogenous" promoter claimed is limited to a promoter that is exogenous to adenovirus, to the patient or the DNA encoding the cytokine.

Claims 15 and 24-26 are indefinite because it is unclear if the "promoter present in said replication-defective adenoviral vector" is present before or after deletion of E1A, E1B and E3. It cannot be determined if the E1A, E1B and E3 are being deleted; therefore, it cannot be determined which adenoviral promoters are encompassed by the claim. Claim 26 is included because it requires the adenovirus lacks E1A and E1B while having an early promoter. Since E1A and E1B are early regions having an early promoter, it is unclear how the vector can have an early promoter.

Overall, it cannot be determined what promoters are excluded from the claim because it is unclear how the description of the promoter limits the claim.

Claim 16 remains indefinite because it does not further limit claim 15. An adenoviral vector cannot lack the E1A region as in claim 15 while retaining the early promoter of the E1A region as in claim 16. Applicants argue a "skilled artisan knows that a promoter is 5' upstream of the coding region but downstream of the operator. The promoter is the region to which an RNA polymerase molecule binds to initiate transcription. The E1A region of the adenovirus is the first viral transcription unit to be expressed and is controlled by the active promoter upstream from this region. Hence, it is possible to have the E1A region deleted and still retain the upstream promoter." Applicants argument is not persuasive. Claim 15 is not limited to a partial deletion of E1A, a deletion in the E1A coding region or a deletion of the E1A region that retains the E1A promoter. Claim 15 requires the vector lacks the E1A region. Since the E1A region is made up of the coding and non-coding (promoter) regions, claim 15 requires the deletion of the entire E1A region including the E1A promoter. Therefore, the vector cannot comprise the E1A promoter as in claim 16 while lacking the E1A region as required in claim 15.

Claim Rejections - 35 USC § 103

The rejection of claims 15-18 under 35 U.S.C. 103(a) as being unpatentable over Nabel (US Patent 6,297,219, Oct. 2, 2001) in view of Crystal (US Patent 6,013,638, Jan. 11, 2000) has been withdrawn because 40-50% tumor regression as claimed was not expected by the combined teachings of Nabel and Crystal.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER